

Dietary baked egg accelerates resolution of egg allergy in children

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Background: Baked egg is tolerated by a majority of egg-allergic children.

Objective: To characterize immunologic changes associated with ingestion of baked egg and evaluate the role that baked egg diets play in the development of tolerance to regular egg.

Methods: Egg-allergic subjects who tolerated baked egg challenge incorporated baked egg into their diet. Immunologic parameters were measured at follow-up visits. A comparison group strictly avoiding egg was used to evaluate the natural history of the development of tolerance.

Results: Of the 79 subjects in the intent-to-treat group followed for a median of 37.8 months, 89% now tolerate baked egg and 53% now tolerate regular egg. Of 23 initially baked egg-reactive subjects, 14 (61%) subsequently tolerated baked egg and 6 (26%) now tolerate regular egg. Within the initially baked egg-reactive group, subjects with persistent reactivity to baked egg had higher median baseline egg white (EW)-specific IgE levels (13.5 kU_A/L) than those who subsequently tolerated baked egg (4.4 kU_A/L; $P = .04$) and regular egg (3.1 kU_A/L; $P = .05$). In subjects ingesting baked egg, EW-induced skin prick test wheal diameter and EW-, ovalbumin-, and ovomucoid-specific IgE levels decreased significantly, while ovalbumin- and ovomucoid-specific IgG₄ levels increased significantly. Subjects in the per-protocol group were 14.6 times more likely than subjects in the comparison group ($P < .0001$) to develop regular egg tolerance, and they developed tolerance earlier (median 50.0 vs 78.7 months; $P < .0001$).

Conclusion: Initiation of a baked egg diet accelerates the development of regular egg tolerance compared with strict avoidance. Higher serum EW-specific IgE level is associated with persistent baked and regular egg reactivity, while initial baked egg reactivity is not. (J Allergy Clin Immunol 2012;130:473-80.)

Key words: Egg allergy, baked egg, heated egg, food allergy, egg tolerance, oral food challenge, egg oral immunotherapy

Egg allergy affects an estimated 1.8% to 2% of children younger than 5 years.¹ A recent study from Australia reported 8.9% prevalence of challenge-proven allergy to uncooked egg in a large cohort of infants younger than 12 months.² While 80% of children eventually outgrow egg allergy, and most in the general population do so by school age, studies indicate that many children evaluated at referral centers are retaining egg allergy into their teenage years.³⁻⁵ It appears that the longer the egg allergy persists, the less likely tolerance will develop.⁴ Thus, it has become imperative to understand individualized prognosis of egg allergy and develop clinical management that will improve the quality of life of egg-allergic children and, ideally, promote earlier tolerance development.

Food processing alters protein structure and affects allergenicity. Previous studies indicated that some egg-allergic individuals tolerate baked egg.⁶⁻⁹ Heating may decrease allergenicity by destroying conformational epitopes or blocking epitope access through interactions with the food matrix (eg, wheat flour), as seen in egg and milk.¹⁰ Children with IgE antibodies predominantly against conformational ovomucoid (OVM) epitopes are more likely to have transient allergy as opposed to those with IgE antibodies against sequential epitopes not altered by heating.^{11,12} Indeed, studies have shown that baked egg tolerance occurs prior to regular egg tolerance.^{7,13}

In the clinical trials conducted at our center, 70% to 75% of egg- and milk-allergic children tolerated baked egg or milk, respectively.^{14,15} In the above-mentioned population-based study conducted in Australia, 80.3% of the children with challenge-proven raw egg allergy tolerated a baked egg challenge.² We recently reported that inclusion of baked milk accelerates resolution of milk allergy.¹⁶ In the initial phase of the baked egg study, we confirmed that baked egg is well tolerated and associated with decreasing egg white (EW)-induced skin prick test (SPT) wheal diameter and serum ovalbumin (OVA)-specific IgE level, and increasing serum OVA- and OVM-specific IgG₄ levels. These immunologic changes parallel those seen in the natural resolution of egg allergy and associated with food oral immunotherapy (OIT).^{5,17-19} In this article, we present long-term immunologic changes and clinical outcomes of egg-allergic children who included baked egg in their diet. We evaluate predictors of baked and regular egg tolerance and assess

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This project has been supported by National Institutes of Health–National Institute of Allergy and Infectious Diseases grant AI 059318 to A.N.-W. and grant no. U11-RR-029887 from the National Center for Research Resources, a component of the National Institutes of Health.

Disclosure of potential conflict of interest: H. A. Sampson has consultant arrangements with Allertein Therapeutics, LLC; serves on advisory boards for ImmusanT and Novartis; received research support from the Food Allergy Initiative and the National Institutes of Health–National Institute of Allergy and Infectious Diseases; is a consultant/scientific advisor for the Food Allergy Initiative; is a medical advisor for the Food Allergy & Anaphylaxis Network; is a scientific advisor for the University of Nebraska–Food Allergy Research and Resource Program and for the Asthma & Allergy Foundation of America; and is 45% owner of Herb Springs, LLC. S. H. Sicherer has consultant arrangements with the Food Allergy Initiative; has received research support from the National Institute of Allergy and Infectious Diseases; and is a medical advisor for the Food Allergy & Anaphylaxis Network. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 20, 2012; revised May 8, 2012; accepted for publication June 6, 2012.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2012.06.006>

Abbreviations used

EoE: Eosinophilic esophagitis
 EW: Egg white
 OFC: Oral food challenge
 OIT: Oral immunotherapy
 OVA: Ovalbumin
 OVM: Ovomucoid
 SPT: Skin prick test

whether the ingestion of baked egg reduces the time to the development of regular egg tolerance.

METHODS**Participants**

Subjects between 0.5 and 25 years of age with documented IgE-mediated egg allergy were recruited from the pediatric allergy clinics at the Mount Sinai Medical Center in New York, NY. Documented IgE-mediated egg allergy was defined by a positive EW SPT result and/or detectable (≥ 0.35 kU_A/L) serum EW-specific IgE level, and a recent history (within the past 6 months) of a type I hypersensitivity reaction to egg or a positive physician-supervised oral food challenge (OFC) to egg; or, if no history of recent reaction, a serum EW-specific IgE level greater than 2 kU_A/L in children younger than 2 years or greater than 7 kU_A/L in children older than 2 years.^{3,20} Subjects were excluded from the study if they had a negative SPT result and undetectable serum EW-specific IgE level, a recent (within the past 6 months) type I hypersensitivity reaction to baked egg, already tolerated and were ingesting baked egg, or a history of eosinophilic esophagitis (EoE), unstable asthma, or pregnancy. The study was approved by the Mount Sinai Institutional Review Board, and informed consent was obtained before enrollment.

Design

Tolerance to baked egg (muffin and waffle) was determined by OFC as previously described.¹⁴ Subjects tolerant to baked egg were challenged with regular egg. Regular egg-tolerant subjects were instructed to incorporate all forms of egg into their diet and were encouraged to do so at least twice a week. Baked egg-tolerant subjects were instructed to incorporate baked egg products into their diets. Baked egg-reactive subjects were instructed to strictly avoid all forms of egg.

Active group

Subjects in the active group were categorized as baked egg-tolerant or baked egg-reactive. Subjects tolerant to baked egg were advised to consume 1 to 3 servings of baked egg per day and avoid regular egg as previously described.¹⁴ Subjects ingesting baked egg were reevaluated every 3 to 12 months, and after 6 months or more were offered challenges to regular egg. Subjects reactive to baked egg were offered repeat challenges to baked egg after 12 months or more.

Immunologic evaluation

SPTs were performed as previously described.²¹ A serum sample was collected at each visit to measure EW-, OVA-, and OVM-specific IgE and OVA- and OVM-specific IgG₄ levels by using UniCAP (Phadia, Uppsala, Sweden).

Oral food challenges

OFCs were performed openly under physician supervision in the Mount Sinai Clinical Research Center. During baked egg challenges, a muffin and a waffle each containing one third of an egg (2.2 g of egg protein) were administered.¹⁴ (See Fig E1 for baked-egg muffin recipe in this article's Online Repository at www.jacionline.org.) Baked egg-tolerant subjects were

challenged to regular egg if their test results were less than the 95% positive predictive values for a positive OFC result: EW-specific IgE level less than 2 kU_A/L in children younger than 2 years or less than 7 kU_A/L in children older than 2 years, or an EW SPT wheal diameter less than 8 mm.^{3,20,22,23} For regular egg challenges, scrambled egg or French toast was administered (1 egg or 6.5 g of egg protein) as per routine protocol.²⁴

Comparison group

We retrospectively identified comparison egg-allergic subjects who were age-, sex-, and IgE-matched with active subjects at the time of enrollment. The same inclusion and exclusions criteria were used, and none of the control subjects had tolerated or were ingesting baked egg at the time of enrollment. Subjects in the comparison group continued strict egg avoidance (current standard of care).²⁵ If they added baked egg to their diet, it was due to accidental exposures. They were challenged to regular egg as per their allergist's recommendation.

Statistics

All statistical analyses were performed with SAS Version 9.2 (SAS Institute, Inc, Cary, NC). A Wilcoxon rank-sum test was used to compare medians of continuous measures, whereas the χ^2 test (and the Fisher exact test when the expected cell count was <5) was used to compare distributions of categorical measures between various subject groups. A Wilcoxon signed-rank test was used to compare medians of continuous measures at different time points. Logistic regression models with nominal (using a generalized logit link function) and ordinal (using a cumulative logit link function) outcomes were used to estimate odds ratios, corresponding 95% CIs, and *P* values with adjustment for sex, age, and initial IgE values. Probabilities of regular egg tolerance were estimated with the Kaplan-Meier product limit method, with comparison among groups evaluated with the log-rank test statistic. The Cox proportional hazards model was used to estimate hazard ratios, corresponding 95% CIs, and *P* values with adjustment for sex, age, and initial IgE values. All statistical hypothesis testing was performed at the .05 level of significance.

Intent-to-treat versus per-protocol analysis

The intent-to-treat analysis includes 79 subjects who underwent the initial baked egg challenge, were available for follow-up, and either reacted to baked egg or regular egg, or tolerated baked egg but had immunologic indications of greater than 95% risk of reaction to regular egg.^{3,20} The per-protocol analysis includes those subjects (*n* = 70) who were, or eventually became, tolerant to baked egg over the course of the study and underwent treatment by adding baked egg to their diet (Fig 1).

RESULTS**Baseline clinical characteristics**

Between June 2004 and September 2007, 117 subjects were enrolled in the study. Detailed baseline characteristics at the time of enrollment were previously described.¹⁴ Briefly, 79 subjects (71% males) were included in the intent-to-treat group, with a median age of 5.8 years (range, 1.6-15.8) and a median initial serum EW-specific IgE level of 2.5 (range, 0.2-101), and were followed for a median of 37.8 months (range, 7.6-69.7). At baseline challenge, 56 (71%) subjects in the intent-to-treat group were baked egg-tolerant and 23 (29%) were baked egg-reactive (Fig 1). The remaining 38 of the 117 subjects initially enrolled and challenged were not included in the analysis because they tolerated regular egg at baseline challenge (*n* = 24), refused to ingest the entire baked egg serving resulting in an inconclusive baseline challenge (*n* = 3), developed subsequent non-IgE-mediated intolerance to egg (*n* = 1), were lost to follow-up after the baseline baked egg challenge (*n* = 3), or passed the baseline baked egg challenge but regular

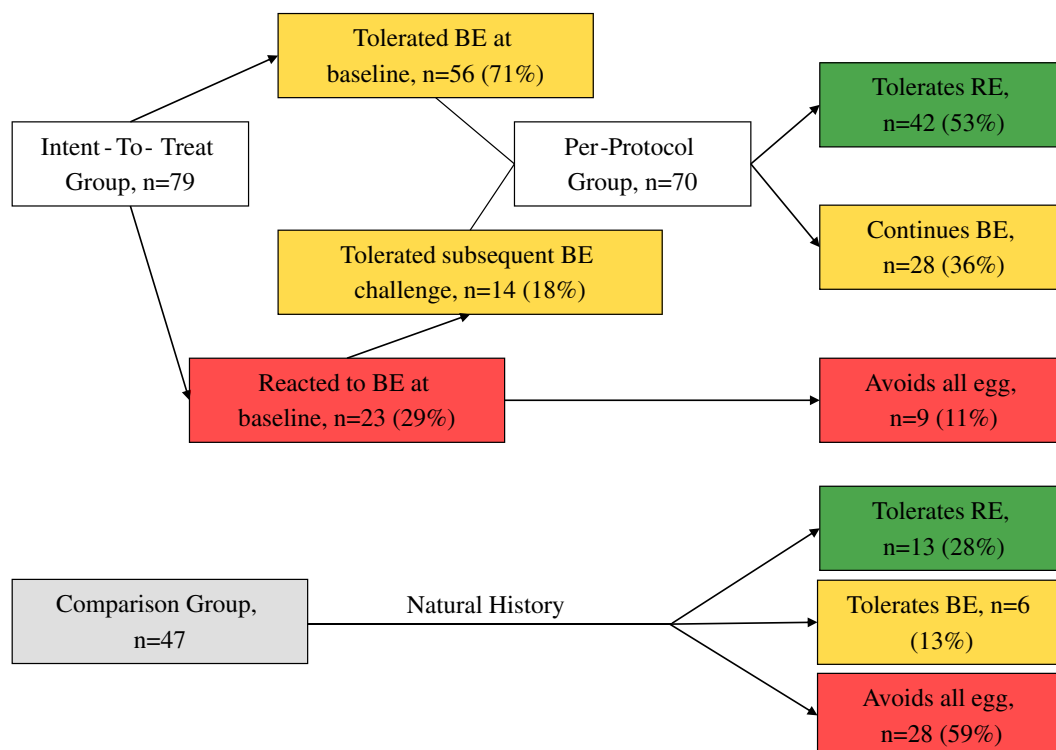


FIG 1. Clinical outcomes of intent-to-treat and comparison groups. BE, Baked egg; RE, regular egg.

egg allergy was not confirmed ($n = 7$; of these, 6 subsequently passed a regular egg challenge).

Clinical outcomes

Overall, 70 (89%) subjects in the intent-to-treat group ($n = 79$) tolerated baked egg over the length of the study, and 42 (53%) now tolerate regular egg with a median time to tolerance of 52.4 months (range, 7.6-67.5 months) (Fig 1). The remaining 9 (11%) continued to avoid egg strictly.

Progression to regular egg tolerance

Of the 56 subjects in the initially baked egg-tolerant group, 36 (64%) now tolerate regular egg. Of the 23 subjects in the initially baked egg-reactive group, 18 were rechallenged a second time and 4 were rechallenged a third time. Fourteen (61%) subsequently tolerated baked egg, and 6 (26%) now tolerate regular egg. Two of the 5 initially baked egg-reactive subjects who were not rechallenged had subsequent reactions to accidental exposures of egg in processed foods.

Subjects in the intent-to-treat group who initially tolerated baked egg were 12.2 times more likely to develop tolerance to regular egg than subjects in the intent-to-treat group who initially reacted to baked egg (95% CI, 3.7-40.3; $P < .001$) (Table I). In contrast, subjects in the per-protocol group who initially tolerated baked egg were not significantly more likely to develop tolerance to regular egg than were subjects in the per-protocol group who initially reacted to baked egg. In other words, once initially baked egg-reactive subjects became baked egg tolerant, they were just as likely as the initially baked egg-tolerant subjects to develop tolerance to regular egg. Overall, subjects in the intent-to-treat

TABLE I. Odds ratios of clinical outcome comparing initially baked egg-tolerant versus initially baked egg-reactive groups, adjusted for sex, age at initial visit, and baseline serum EW-specific IgE

EW-specific IgE		
Clinical outcome	BE tolerant vs BE reactive intent-to-treat, OR (95% CI)	P value
Regular egg tolerant*	12.2 (3.7-40.3)	<.001
BE tolerant vs BE reactive per-protocol, OR (95% CI)		
Regular egg tolerant†	3.1 (0.8-11.2)	.092

The intent-to-treat group consists of all subjects enrolled in the active arm of the study, including baked egg-reactive subjects. The per-protocol group consists of children in the active group who were, or eventually became, tolerant to baked egg over the length of the study.

OR, Odds ratio.

*The reference group is composed of patients avoiding regular egg or all egg products.

†The reference group is composed of patients avoiding regular egg as there were no patients avoiding all egg products in the per-protocol group.

group who initially tolerated baked egg were 3.3 times more likely to develop regular egg tolerance than subjects initially reactive to baked egg over the follow-up period (hazard ratio, 3.3; 95% CI, 1.2-8.9; $P = .017$) (Fig 2).

Time to regular egg tolerance

Initially baked egg-tolerant subjects developed regular egg tolerance significantly earlier than initially baked egg-reactive subjects. The median time to regular egg tolerance

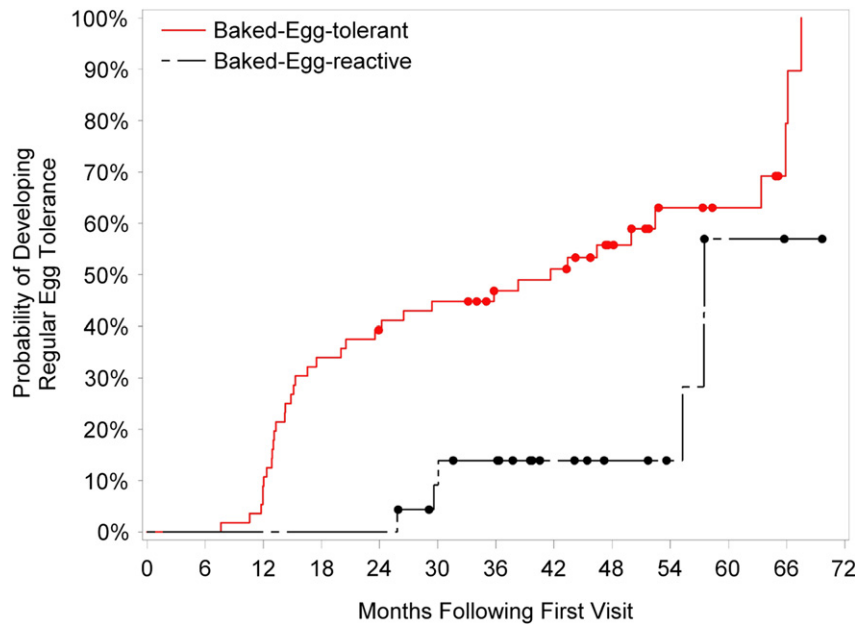


FIG 2. Development of regular egg tolerance in the intent-to-treat group stratified by initial baked egg challenge: tolerant versus reactive. The log-rank *P* value comparing time to development of tolerance between the initially baked egg-tolerant versus initially baked egg-reactive groups is .004.

was 41.7 months in the initially baked egg-tolerant group versus 57.5 months in the initially baked egg-reactive group ($P = .004$).

Immunologic parameters in subjects ingesting baked egg

Baked egg-tolerant subjects had lower baseline EW-specific IgE levels than baked egg-reactive subjects: median 1.9 kU_A/L (interquartile range [IQR], 0.6-6.1; range, 0.0-101) versus 13.5 kU_A/L (IQR, 5.9-18.9; range, 2.8-58.9) ($P = .002$). Baked egg-tolerant subjects also had smaller baseline EW-induced SPT wheal diameters than baked egg-reactive subjects: median 6 mm (IQR, 5-8; range, 0-19) versus 8 mm (IQR, 8-9; range, 7-15) ($P = .005$). EW-induced SPT wheal diameter and EW-, OVA-, and OVM-specific IgE levels all decreased significantly from baseline in subjects ingesting baked egg ($P < .0001$, $P < .0001$, $P < .0001$, and $P = .0002$, respectively) (Table II). OVA- and OVM-specific IgG₄ levels increased significantly (both $P < .0001$), and the ratio of OVA and OVM IgE/IgG₄ decreased significantly ($P = .0003$ and $P < .0001$, respectively) from baseline in subjects ingesting baked egg.

Characteristics of children with persistent reactivity to baked egg

Within the group of initially baked egg-reactive subjects, those with persistent baked egg reactivity had significantly higher median baseline EW-specific IgE levels (13.5 kU_A/L) than did those who subsequently tolerated baked egg (4.4 kU_A/L; $P = .04$) and regular egg (3.1 kU_A/L; $P = .05$) (Table III). Final EW-specific IgE levels were greater and final EW-induced SPT wheal diameters were larger in subjects with persistent baked egg reactivity than in subjects initially reactive to baked egg who subsequently tolerated baked egg ($P = .02$ for both) and

TABLE II. Immunologic parameters of the per-protocol group and subgroup that eventually tolerated regular egg, expressed as median (25%-75% IQR)

	Baseline per-protocol	Last follow-up per-protocol	<i>P</i> value
SPT (mm), n = 46	6 (4.5-8)	4 (2.3-5)	<.0001
EW IgE (kU _A /L), n = 64	2.1 (0.6-6.4)	0.9 (0.0-2.3)	<.0001
OVA IgE (kU _A /L), n = 45	1.9 (0.6-6.1)	0.9 (0.0-2.2)	<.0001
OVA IgG ₄ (kU _A /L), n = 46	0.5 (0.1-1.6)	2.6 (0.6-9.2)	<.0001
OVA IgE/G ₄ *, n = 36	3.9 (1.1-20.3)	0.3 (0.0-2.5)	.0003
OVM IgE (kU _A /L), n = 45	1.0 (0.0-2.7)	0.4 (0.0-1.3)	.0002
OVM IgG ₄ (kU _A /L), n = 46	0.0 (0.0-0.4)	0.4 (0.1-1.5)	<.0001
OVM IgE/G ₄ *, n = 20	5.6 (1.0-12.5)	0.8 (0.0-1.9)	<.0001
	Baseline of subgroup who tolerated RE	Subgroup at time of RE tolerance	<i>P</i> value
SPT (mm), n = 41	6 (5-8)	3 (2.5-5)	<.0001
EW IgE (kU _A /L), n = 40	1.3 (0.6-4.4)	0.6 (0.0-1.5)	.0003
OVA IgE (kU _A /L), n = 29	1.5 (0.5-3.1)	0.5 (0.0-1.2)	<.0001
OVA IgG ₄ (kU _A /L), n = 29	0.5 (0.0-1.6)	4.4 (1.9-10.0)	<.0001
OVA IgE/G ₄ *, n = 23	3.2 (0.5-6.6)	0.0 (0.0-0.6)	<.0001
OVM IgE (kU _A /L), n = 29	0.9 (0.0-2.8)	0.0 (0.0-0.6)	<.0001
OVM IgG ₄ (kU _A /L), n = 29	0.1 (0.0-0.5)	0.6 (0.1-1.3)	<.0001
OVM IgE/G ₄ *, n = 16	5.3 (0.6-10.8)	0.4 (0.0-1.6)	.0002

BE, Baked egg; RE, regular egg.

*Denominator (IgG₄) 0 in many cases.

regular egg ($P = .01$ and $P = .02$, respectively). Two of the 4 initially baked egg-reactive subjects who were treated with epinephrine during the baseline baked egg challenge were still strictly avoiding egg at the end of the study, compared with 7 of 19 (37%) initially baked egg-reactive subjects who did not receive epinephrine during the baseline baked egg challenge (χ^2 test, $P = .05$).

TABLE III. Baseline and final EW-induced SPT and EW-specific IgE of the initially baked egg–reactive group based on clinical outcome, expressed as median (25%-75% IQR)

	Avoids all egg (n = 9)	Subsequently tolerated BE (n = 14)	P value	Subsequently tolerated RE (n = 6)	P value
SPT (mm)					
Baseline	8 (8-9)	7.5 (6-9)	.13	6.5 (6-9)	.19
Final	8 (6-10)	4 (2.5-5.5)	.02	2.8 (1.5-4.5)	.02
EW IgE (kU _A /L)					
Baseline	13.5 (5.9-18.9)	4.4 (1.9-8.8)	.04	3.1 (1.2-4.4)	.05
Final	5.4 (3.3-25.4)	1.8 (1.1-3.5)	.02	0.9 (0.6-1.1)	.01

BE, Baked egg; RE, regular egg.

TABLE IV. Odds ratios of clinical outcome comparing per-protocol and intent-to-treat versus comparison groups, adjusted for sex, age at initial visit, and EW-specific IgE

Clinical outcome	Vs	Per-protocol vs comparison, OR (95% CI)	P value
Regular egg tolerant	Avoiding all egg	18.3 (5.5-60.9)	<.0001
	BE tolerant	0.9 (0.3-2.8)	.817
BE tolerant	Avoiding all egg	20.9 (5.8-76.2)	<.0001
		Intent-to-treat vs comparison, OR (95% CI)	
Regular egg tolerant	Avoiding all egg or BE tolerant	4.7 (1.9-11.5)	.0006

BE, Baked egg; OR, odds ratio.

Comparison group

The comparison group consisted of 47 subjects (66% males) with a median age of 4.6 years (range, 1.7-20.9 years) and a median initial serum EW-specific IgE level of 4.8 (range, 0.2-58) who were evaluated in our clinic during the period of study enrollment and followed for a median of 67.3 months (range, 40.5-81.8). Baseline age, sex, and initial EW-specific IgE levels were not significantly different between the intent-to-treat and comparison groups. The comparison group was followed for a significantly longer time than the intent-to-treat group (median 67.3 vs 37.8 months; $P < .0001$). A majority (59%) of the comparison group was strictly avoiding egg at the end of the study period, while 13% were baked egg–tolerant and 28% were regular egg–tolerant (Fig 1). Subjects who underwent active treatment (the per-protocol group, which excludes those with persistent baked egg reactivity) developed regular egg tolerance significantly earlier than did those in the comparison group. The median time to regular egg tolerance was 50.0 months in the per-protocol group versus 78.7 months in the comparison group ($P < .0001$). Subjects who developed regular egg tolerance in the per-protocol group were slightly older at baseline compared with their counterparts in the comparison group (median 5.5 vs 4.5 years; $P = .048$).

Subjects in the per-protocol group were 20.9 times more likely to tolerate baked egg (95% CI, 5.8-76.2; $P < .0001$) and 18.3 times more likely to tolerate regular egg (95% CI, 5.5-60.9; $P < .0001$) than the comparison group (Table IV). This significance is maintained when comparing the intent-to-treat and comparison groups (OR 4.7; 95% CI, 1.9-11.5; $P = .0006$). Overall, subjects in the per-protocol group were 14.6 times more likely to develop regular

egg tolerance than subjects in the comparison group over the follow-up period (hazard ratio, 14.6; 95% CI, 5.8-36.4; $P < .0001$) (Fig 3).

Tolerability of baked egg diet

Baked egg was well tolerated without reports of acute allergic reactions to baked egg at home or worsening of eczema or asthma. One subject initially reactive to baked egg passed a baked egg rechallenge, then subsequently developed vomiting and diarrhea hours after accidental exposures to regular egg (in icing and cookie dough ice cream). This reaction was consistent with atypical food protein–induced enterocolitis syndrome, and this child reverted to complete egg avoidance. None of the subjects developed EoE.

Withdrawals

Three subjects initially reactive to baked egg in the intent-to-treat group were lost to follow-up. Eighteen subjects initially tolerant to baked egg withdrew from the study by 1 year¹⁴; however, we were able to follow-up with these subjects by telephone and confirm that they were continuing to ingest baked egg or had become tolerant to regular egg.

DISCUSSION

While avoidance continues to be the safest way to prevent symptoms of allergic food reactions, reports of food-sensitized eczema patients who developed systemic reactions after a period of avoidance and the recurrence of peanut allergy in former peanut-allergic patients who ingested peanut infrequently or in limited amounts have begun to change our way of thinking about tolerance.²⁶⁻³⁰ There is an increasing interest in OIT with native (unmodified) protein for the treatment of food allergy, and several clinical trials have shown promising results as subjects were able to tolerate increased amounts of the offending food.^{19,31-34} However, adherence to OIT suffers from the relatively high prevalence of adverse side effects.³⁵ Baked egg may represent an alternative and safer method of introducing allergens into the diets of egg-allergic individuals with the goal of improving quality of life and accelerating the resolution of their allergy.

We report that 89% (70 of 79) of the subjects now tolerate baked egg and 53% (42 of 79) now tolerate regular egg over a median of 37.8 months of follow-up. In addition to the 70% of subjects who tolerated baked egg at the baseline OFC as we previously reported, we found that a majority of subjects initially reactive to baked egg subsequently developed tolerance to baked

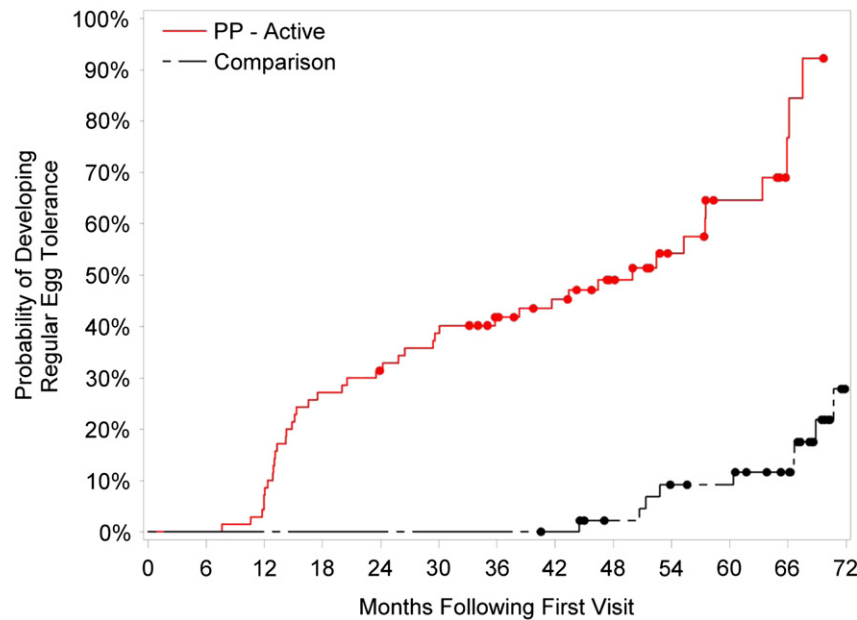


FIG 3. Development of regular egg tolerance: per-protocol (PP) versus comparison groups. The log-rank *P* value comparing survival between the PP versus comparison groups is less than .0001.

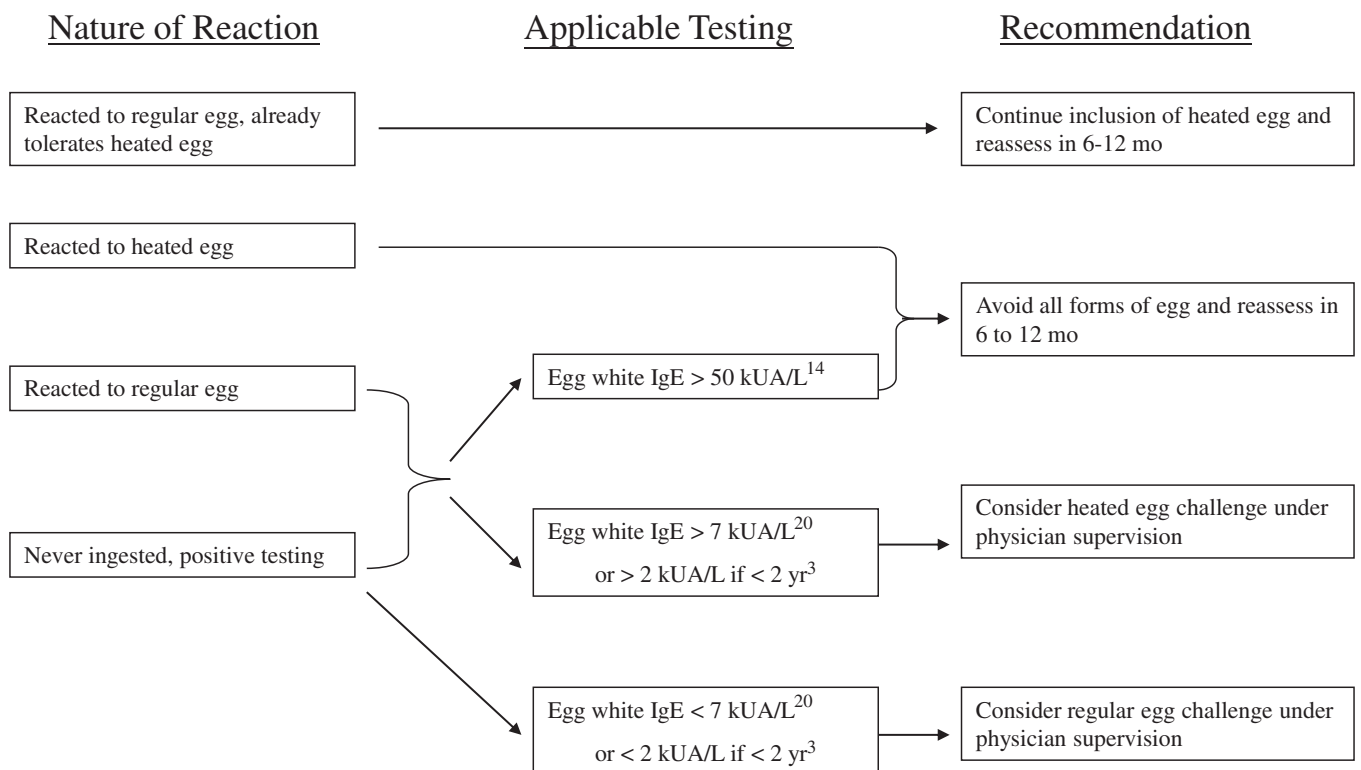


FIG 4. Criteria for selecting patients for baked and regular egg challenges.

egg over the follow-up period and some of them now tolerate regular egg. This is in contrast to what we reported in the baked milk study, where initial baked milk reactivity was a predictor of persistent baked and unheated milk reactivity.¹⁶ Instead, higher baseline serum EW-specific IgE level in the initially baked egg-reactive group was associated with persistent baked and regular egg reactivity.

We previously reported a decrease in EW-induced SPT wheal diameter and serum OVA-specific IgE level and an increase in serum OVA- and OVM-specific IgG₄ levels after 3 months of ingesting baked egg.¹⁴ Here we report that long-term ingestion of baked egg is associated with significantly decreasing serum whole and component egg-specific IgE levels and sustained changes in SPT wheal diameter and serum component IgG₄ levels.

We followed our subjects for up to 6 years and confirmed that continued ingestion of baked egg in the diet of egg-allergic children was well tolerated. Even those patients who withdrew from the study or reported an increase in eczema (not confirmed by exam) by 1 year continued to ingest baked egg regularly in their diet years later. Despite reports of EoE developing in children who had undergone OIT, none of our patients developed EoE.^{36,37} We observed 1 subject with a history of immediate IgE-mediated symptoms to baked egg develop delayed gastrointestinal symptoms hours after accidental exposure to regular egg, which is consistent with atypical food protein-induced enterocolitis syndrome.³⁸ This occurred after the subject passed a baked egg challenge and began to ingest baked egg regularly. It is unknown whether a baked egg diet may have predisposed this subject to developing food protein-induced enterocolitis syndrome-like symptoms.

Regular egg tolerance was achieved in a greater proportion of the active study group and earlier than the comparison group ($P < .0001$). This may be an underestimation of the difference considering that the comparison group was followed for a significantly longer time period, giving these subjects more time to naturally outgrow their egg allergy. It appears that the approach of adding baked egg to the diets of egg-allergic children who can tolerate baked egg accelerates the induction of regular egg tolerance. Alternatively, the shorter time to tolerance might reflect close follow-up of subjects within the active study group and a more proactive pursuit of diagnostic challenges to regular egg. Having a retrospective comparison group is one of the limitations of our study. However, we recently reported that among 100 unselected open baked egg challenges done in our office in patients with median age 5.9 years (range, 1.2–19.8 years), 66% tolerated baked egg.³⁹ Therefore, we feel reassured that the retrospective comparison group derived from our patient base was sufficiently comparable to the study subjects.

Clark et al¹³ recently reported in a longitudinal study of 95 young children that egg-allergic subjects were able to tolerate well-cooked egg at a median age of 5.6 years and uncooked egg at 10.3 years. Epinephrine was not administered during any OFC in the study, although 9 subjects experienced respiratory symptoms during uncooked egg challenges and 3 received nebulized bronchodilators. In our cohort, 19% of baked egg–reactive subjects and 23% of baked egg–tolerant but regular egg–reactive subjects experienced mild anaphylaxis that was treated with intramuscular epinephrine.¹⁴ This argues against the notion that tolerance of baked egg products reliably predicts milder reactions to regular egg and highlights the difficulty of predicting baked egg tolerance based on the history of reaction severity to regular egg.

In conclusion, the results of our study indicate that the majority of subjects with egg allergy tolerate baked egg and that long-term ingestion of these products is well tolerated and accelerates the development of tolerance to regular egg. Ingestion of baked egg is associated with immunologic changes, including decreasing EW-induced SPT wheal diameter and EW-specific IgE levels. Higher baseline EW-specific IgE levels are associated with baked and regular egg reactivity, while initial baked egg reactivity is not. We propose that for as many as 89% of the egg allergic–children, the ingestion of baked egg products is a safer, more convenient, less costly, and less labor-intensive form of oral immunomodulation.

While our data are encouraging for improving the quality of life and hastening the tolerance of regular egg for a majority of egg-allergic children, oral challenges to baked egg must be

undertaken under physician supervision with all precautions typically used when performing food challenges in children. Egg allergy phenotypes and markers of baked egg tolerance have not been fully defined, and the safety of home introduction of baked egg has not been validated.⁴⁰ Our study shows that anaphylaxis to baked egg occurs and is not easily predicted. The British Society for Allergy and Clinical Immunology recently published recommendations for home reintroduction of well-cooked (baked) egg; however, the new guidelines by the National Institute of Allergy and Infectious Diseases–sponsored expert panel in the United States did not incorporate the introduction of baked egg into the recommendations regarding the management of egg allergy.^{25,41} Further studies are required to more clearly define which egg-allergic patients can safely tolerate and benefit from the inclusion of baked egg in their diets. Until such studies are completed, the introduction of baked egg into the diet of those strictly avoiding egg should be undertaken with physician supervision. Our proposed guidelines for the introduction of baked egg into the diets of egg-allergic children can be found in Fig 4.

We thank Ramon Benchritiwig, PhD, for technical assistance in the lab, Shideh Mofidi, RD, for development of food challenge recipes, and Joanna Lis, BA, and Natasha Setia, MS, for assistance with telephone follow-up.

Clinical implications: Addition of dietary baked egg is safe, convenient, and well accepted by patients. Introducing baked egg to egg-allergic children presents an important shift in the treatment paradigm for egg allergy.

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Yield: 6 muffins (1/3 egg per muffin)

Ingredients:

1 cup all-purpose flour (or flour substitute)
¼ teaspoon salt
2 tablespoon cow's milk (or soy milk, rice milk, almond milk)
1 teaspoon baking powder
¼ teaspoon cinnamon
2 eggs
½ cup sugar
¼ cup corn oil
½ teaspoon vanilla
1 cup mashed ripe banana or applesauce

Directions:

1. Preheat oven to 350 degrees.
2. Line a muffin pan with 6 muffin liners.
3. Mix together the liquid ingredients: milk or milk substitute, canola oil, vanilla extract, mashed ripe banana or applesauce and eggs. Set aside.
4. In a separate mixing bowl, mix together the dry ingredients : flour or flour substitute, sugar, salt, cinnamon, baking powder.
5. Add the liquids ingredients to the dry ingredients. Stir until combined. Some small lumps may remain.
6. Divide the batter into the six prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin liners all the way to the top. If you make more than 6 muffins, please note how many muffins you made and bring at least two muffins with you on the day of the challenge.
7. Bake for 30 to 35 minutes or until golden brown and firm to the touch.

FIG E1. Baked-egg muffin recipe developed at the Jaffe Food Allergy Institute.